[1662/61702]

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicants	:	Liberman et al.
Serial No.	:	10/717,325
Filed	:	November 18, 2003
For	:	STABLE LANSOPRAZOLE CONTAINING MORE THAN 500 PPM, UP TO ABOUT 3,000 PPM WATER AND MORE THAN 200 PPM, UP TO ABOUT 5,000 PPM ALCOHOL
Examiner	:	Morris, Patricia L.
Art Unit	:	1625

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

DECLARATION UNDER 37 C.F.R. § 1.131

Sir:

We, Claude Singer, Anita Liberman, and Irena Veinberg , declare and state as follows:

1. We are the named inventors of the above-identified application, and are also named inventors of U.S. Patent Application Publication No. 2004/0192923 ("the '923 application").

2. We conceived of the subject matter described and claimed in the above-identified application prior to October 11, 2002, and, more particularly, prior to August 21, 2002.

3. Attached hereto as Exhibit 1 is a copy of an Invention Disclosure Document entitled "NEW METHOD FOR THE PURIFICATION OF LANSOPRAZOLE," which was prepared and submitted to patent counsel for Teva Pharmaceutical Industries, Ltd., ("Teva"), the assignee of the entire right, title, and interest in and to the above-identified application, prior to October 11, 2002, and, more particularly, prior to August 21, 2002, with an "Order Letter" and "Fax Coversheet." Copies of the Order and Fax Coversheet are also attached as part of Exhibit 1.

4. Example 2 of the Invention Disclosure Document demonstrates that we were in possession of the presently claimed chemically stable lansoprazole and a method of preparing the chemically stable lansoprazole of the claimed invention at a time prior to October 11, 2002, and, more particularly, prior to August 21, 2002.

5. We exercised diligence in constructively reducing to practice the subject matter described and claimed in the above-identified application from at least a time prior to October 11, 2002, and, more particularly, from a time prior to August 21, 2002, continuously up to February 5,2003, the date on which U.S. Provisional Patent Application No. 60/445,219, the provisional application to which the above-identified application claims benefit was filed in the United States Patent and Trademark Office. During that time, we

provided information to patent counsel for preparation of the provisional application and reviewed and revised drafts thereof.

6. We hereby declare that all statements made herein of our own knowledge are true, and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under 35 U.S.C. § 1001, and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

Date: 16.01.06 — Claude Singer

Date: 16.01.06 — Anita Liberman

Date: 19.01.06 — Irena Veinberg

Exhibit 1

TEVA Pharmaceutical Industries Ltd.
Patent Department
PO Box 3190
Petach Tikva 49131
ISRAEL

MAYA SEGAL
E-mail: maya.segal@teva.co.il

Direct Fax: +972-3-926-7484
Direct Phone: +972-3-926-7606

6

FAX COVERSHEET

Date:	[redacted]
To:	**Mr. Patrick Birde**
Re:	**Lanzoprazole – New Application**
Fax No.:	**001-212-425-5288**
No. of Pages: (incl. cover)	*9*

inventors
disclosure

☐ **ORDER LETTER** Date: [redacted]

☐ Title: Lansoprazole - purification

☐ Client Ref.: 4030 p1 K&K Ref:

☐ Assignee: ☒ Teva Ltd. (#1662) ☐ Teva USA (#1907)
☐ Biogal (#2664) ☐ Copley (#11168)
☐ Human RT (#11701) ☐ Novapharm Ltd. (#11473)
☐ Pharmachemie (#10663) ☐ Plus Chemicals (#11128)

☐ Priority Info: ☐ None ☐ Will Follow
☐ Other applications re Lansoprazole

☐ Disclosure ☒ Attached ☐ Will Follow

☐ Inventor(s) In the disclosure

☐ Provisional ☒ Immediate - aim for same day High priority
☐ ASAP - 3-7 Days

☐ Non-Provisional ☐ Inventor Conference If needed - by Lemon
(proposed date)
☐ Target Date:

☐ Contact Person ☐ Kenyon _____

☒ Teva Gadi Cohen

☐ Related Case Info.: _____

☐ Keywords: _____

☐ Comments/Instructions: The disclosed process will be Teva's Scale-up process.

☐ Docketed: _____

167/61001

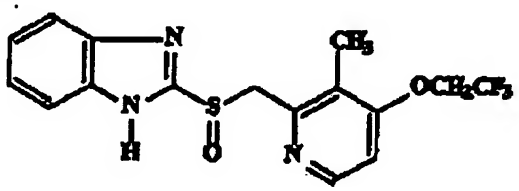
New method for the purification of Lansoprazole

Suggested inventors:

1	Claude Singer	4	Nina Finkelstein
2	Anita Lieberman	5	Tamar Nidam
3	Irena Veinberg		

Related art

Lansoprazole is the generic name of the compound, which has following chemical structure:



Its chemical name is:2- [[[3- methyl- 4-(2,2,2- trifluoroethoxy)- 2- pyridyl] methyl] sulfinyl]-1*H*-benzimidazole

Lansoprazole is a reversible proton (acid) pump inhibitor developed by Takeda as an antiulcer agent. Other compounds with similar biologic activity are Omeprazol and Pantoprazol. Lansoprazol *per se* is protected by US 4628098 owned by Takeda.

Several preparation methods for Lansoprazole were published . In the majority of these methods the precursor of Lansoprazole containing a thioether group is oxidized in the last step forming Lansoprazole. In US 4628098 m- Chloro- Perbenzoic Acid is used for this purpose. In US 5,578,732 it is mentioned that the oxidation with m-Chloro-Perbenzoic Acid is not selective and therefore an oxidation method with H_2O_2 is disclosed in the presence of specific Vanadium catalysts. Other patents such as ES 2105953, WO 0121617, ES 2063705, US 6313303, WO9947514, WO0168594 are using other oxidation reagents and/or other catalysts. However the Lansoprazole formation is always accompanied by the formation of small quantities of the corresponding sulfone derivative as mentioned in US 6180652. The sulfone derivative impurity must be separated from Lansoprazole and this is not a

simple task taking into account the similar structure of Lansoprazole and its sulfone derivative. For this purpose in US 6180652 a method is disclosed which permits the separation of Lansoprazole salt from its sulfone derivative salt. Actually an acetone complex of above mentioned Lansoprazole salt is purified in this method.

Lansoprazole is a relative unstable compound especially in acidic but also under strong basic conditions. US 6002,011 mentions that Lansoprazole after the ethanol-water crystallization, is obtained as solvate, which after intensive drying does not release entirely the above mentioned solvents. As a consequence Lansoprazole is unstable under usual storage conditions. The patent discloses a reslurry method in water which permits to obtain 'solventfree Lansoprazole' which according to above mentioned patent is more stable.

Summary of the present invention

The present invention discloses an alternative crystallization method, which permits an advanced purification of Lansoprazole from its impurities, especially sulfone. In this method during the crystallization from a solvent- water system ammonium hydroxide solution is added in molar quantities and neutralized further with acetic acid during the precipitation of Lansoprazole.

Also a crystallization method to obtain 'solventfree Lansoprazole ' is disclosed.

Detailed description of the invention

In US 5,578,732 the crystallization from the ethanol : water system (9:1) was described. This crystallization has a limited purification effect even if traces of NH_4OH solution (0.03M: M Lansoprazole) are added as suggested in the Examples of US 6002011. It was surprisingly discovered that by increasing significantly the quantity of ammonium hydroxide solution to >1M NH_4OH: 1M of Lansoprazole it is possible to purify significantly Lansoprazole from its impurities especially the sulfone derivative of Lansoprazole mentioned above. The purified product precipitates when acetic acid is added to the Ammonium solution of Lansoprazole.

Ethanol can be replaced by other alcohols such methanol , n- propanol , i- propanol . Other solvents which can be used are acetone , 2- butanone , dimethyl-formamide and tetrahydrofurane.

Ammonium hydroxide can be replaced by amines such as diethylamine , triethylamine and methylamines.

The Acetic Acid used for the precipitation of Lansoprazole can be replaced by other acids such as Formic Acid , HCl.

Different ratios solvent: water can be used varying between 0.2:1 to 3:1. Larger ratios are limited by the poor crystallization yields. Most recommended is the ratio 1.5:1. The overall ratios solvent mixture : Lansoprazole can vary between 17 : 1 to 1:1. Most recommended is the ratio 7:1.

Lansoprazole can be dissolved at the reflux temperature of the solvent mixture. However recommended temperatures are lower than the reflux temperature given the instability of Lansoprazole solutions at higer temperatures. The recommended temperatures should not exceed 60°C.

In comparison to US 6180652 this purification procedure has following advantages:

There is no need to transform Lansoprazole into one of its salts prior to the purification process and back into basic drug at the end of the purification.

From the crystallization Lansoprazole is received directly as a pure product and not as an acetone complex which must be transformed back into the basic drug substance

Hydrocarbons and other non-polar solvents necessary for the precipitation of the acetone complex of the Lansoprazole salt must be removed carefully in order to meet the very restrictive specifications for residual solvents.

Pure Lansoprazole is obtained containing <0.1% sulfone and <0.1% starting material (sulfide) which is substantially less than mentioned in

6180652.

Although Lansoprazole obtained by the above mentioned crystallization can be advantageously purified it can not be dried to <0.1% water as required by the USP forum. As mentioned previously this can have a negative impact on the long term stability of Lansoprazole (US 6,002,011). It was discovered that solvent free Lansoprazole can be obtained by the recrystallization of

Lansoprazole from different solvents .

As recrystallization solvents acetone or 2-butanone can be used. Good results were also obtained in methanol , dimethyl-carbonate and diethyl-carbonate. In order to make a successful crystallization it is necessary to dissolve Lansoprazole completely in the corresponding solvent. The dissolution is accelerated by the presence of small amounts of water. The presence of water can be insured by using wet Lansoprazole from the previously mentioned purification step or by adding < 10% water to the corresponding solvent. The dissolution of Lansoprazole in a certain solvent can be performed at reflux however taking into consideration the inherent instability of the product at higher temperatures it is recommended not to exceed >50°C.

The process yield can be improved by cooling or by removing partially the solvent or the azeotrop water-solvent from the system.

Following examples are illustrating the invention:

Example 1

Preparation of Lansoprazole crude

Into a flask 1. L ethanol was charged and cooled under stirring to 5°C. Under mixing 200g 2- [[3- methyl-4- (2,2,2- trifluoroethoxy)- 2- pyridinil]thio]- 1H benzimidazole (LNPS) and 3g Vanadinm acetyl acetonate was added. 110g tert-butyl-hydroperoxide solution was dropped slowly into the suspension. The suspension was maintained under mixing during 4 hours. 40g of Na_2SO_3 dissolved in 400 ml water were added. Separate solid phase by vacuum filtration and dry. 165 g of LNP crude is obtained (yield 79 %). Sulfone 0.3% LNPS 0.3%

Example 2

Purification of Lansoprazole

In a 0.25L flask 67.5ml Ethanol 95% , 15ml of Ammonia 24% and 45ml water was charged and cooled under stirring to 5°C. Under mixing 10g Lansoprazole crude was added and heated to 52° to dissolution . 1g of active carbon was added to the slighly turbid solution and maintained a short time at 49°C. The carbon was separated on a filter and the cake washed with a mixture of 14ml

Ethanol and 12ml water. The solution was cooled and Lansoprazole was precipitated by the addition of 3.75ml Acetic Acid. The suspension was cooled to 10°C and filtered. The product was washed with water and ethanol and dryed. 8.7g of Lansoprazole pure is obtained (yield 89%). Sulfone 0.05% , LNPS under the detection limit.

The above described procedure was applied also in other examples where the solvent and/or the amine was different Following table is illustrative for these examples :

Example	Solvent	water	Amine	Yield	Sulfone	LNPS
		yes/no		%	%	%
3	i-propanol	no	NH_4OH	52.7	0.03	0.02
4	ethanol	no	NH_4OH	46.5	0.07	<DL[1]
5	n-propanol	yes	NH_4OH	91.5	0.08	0.04
6	i-propanol	yes	NH_4OH	90.8	0.07	<DL
7	ethanol	yes	triethylamine	87.6	0.05	<DL

8 i-buthanol yes triethylamine 80.7 0.06 <DL [1] less than detection limit

Example 9

Preparation of 'solventfree Lansoprazole '

In a 0.25L flask 29.8g wet LNP cryst and 30ml Acetone is charged. The suspension is heated to 52°C and 150ml Acetone is dropped until a clear solution is obtained. The solution is cooled to 10°C and concentrated until the weight of the reaction mass is 48.5g. The solid is separated by filtration and washed with 20ml cold Acetone. After drying 18.58g product is obtained (yield 91%). Content of water according to Karl Fischer test 0.05%.

Similar to example 9 following other examples were performed:

Examples

Solvent	Yield	Water	
		%	%(KF[1])
10	dimethylcarbonate	87.5	0.04

11 2-butanone 88.5 0.03 12 methanol 72% 0.06

Claims

urification method of Lansoprazole

ure Lansoprazole containing <0.1% sulfone and <0.1% LNPS

Crystallization method of Lansoprazole for reducing the water content to <0.1% water.